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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/926,358
Filing Date: January 07, 2002
Appellant(s): TAGAWA ET AL.

Bruce H. Bernstein
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 5-15-06 appealing from the Office action mailed 11-15-05.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. The amendment after final has been entered.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

| | | |
|---|---|---|
| **5,264,221** | **TAGAWA et al** | **11-1993** |
| **6,139,869** | **HOSOKAWA et al** | **10-2000** |
| **6,787,153** | **HOSOKAWA et al** | **9-2004** |

**Kirpotin, D et al. "Sterically stabilized anti-HER2 immunoliposomes: Design and targeting to Human breast cancer cells in vitro". Biochemistry, vol. 36 (1997), pp. 66-75.**

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 16-23 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagawa (5,264,221).

Instant claim 16 is drawn to a liposome, which comprises polyalkylene glycol and antibody, both bonded to the liposome surface through thioether groups, wherein the lipids have maleimidated terminal. The amount of the bonded compound according to the claim is 15 to 30 mole percent and the amount of the antibody is 1.2 to 2 mg per 100 mg of total lipids and the antibody is GAH antibody.

Tagawa discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody, GAH) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to

the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin (note the abstract, col. 2, line 45 through col. 5, line 27, Figure 2 and examples). The mol. percent of the bonded compound as disclosed in the reference on col. 4, lines 59-68 appear to fall within the claimed range. The degree of polymerization of PEG is 20-400 as noted from col. 4, line 20 which corresponds to instant molecular weights.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the rejection makes allegations regarding canceled independent claim 10, but does not indicate how Tagawa 221 anticipates applicant's independent claim 16. According to applicant, Tagawa 221 discloses the use of a thiolated antibody in a ratio of 0.1 mole % to 20 mol % based on 1 mol of maleimide group and as explained in Example 3 of Tagawa, the liposome disclosed in Example 3 was prepared according to method of Example 2 which means that 100 mg of lipid was used for preparation of the liposome and in contrast to the liposomes recited in claim 16, Tagawa 221 discloses the preparation of liposomes using 5 mg of Fb' antibody for 100 mg of lipids. Appellant argues that the examiner points to a broader range disclosed by Tagawa and also contends that 4.5 is close to 5. According to appellant, such disclosure should not be considered to be anticipation and is not applicable to claim 16, which discloses 1.2 to 2 mg per 100 mg of total lipids. The examiner disagrees and respectfully directs the board attention to appellant's previous admission (see page 9 of response dated 8-8-05) that 0.1 mole to 20 mol % of antibody in Tagawa 221 corresponds to 0.3 mg to 60 mg. The examiner agrees that this is a broad range, however, in the example, as also admitted by appellant, Tagawa 221 uses 5 mg

antibody which is closer to the lower limit of 0.3 mg and applicant's claimed range of 0.5 to 4.5 % in canceled claim 10 and not far away from 1.2 to 2 mg in claim 16. Thus, although Tagawa 221 teaches a broader range, the example is closer to the claimed range.

Appellant argues that claimed invention relates to liposome having 15 to 30 mole % polyalkylene glycol moiety and Tagawa does not teach such amounts. The examiner disagrees and points out to col. 4, lines 64-66 of Tagawa 221 which indicate that polyalkylene glycol is added in an amount of at least twice in equivalent to the antibody. Since the amount of antibody added is 0.1 % to 20 mole % (col. 4, lines 59-61), at least twice the amount would be 0.2 % to 40 % which range encompasses instant 15 to 30 mole %.

Appellant argues about the unexpected advantages of using smaller amounts of bound antibody, that is, smaller amounts of bound antibody giving a higher therapeutic effect. The examiner respectfully directs the board's attention to appellant's previous arguments in page 17 of the response dated 8-8-05, "A review of Fig. 3 in applicant's application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids". This statement clearly indicates that irrespective of whether the antibody amount is outside the claimed range or inside the claimed range the results are significant meaning that even 221 results are unexpected. Therefore, the reference is still a 102 reference".

Appellant argues that Tagawa 221 does not teach the combination of features as recited in claim 17, which further includes that the liposome is obtained by reacting a maleimide group of the maleimidated lipid with a compound containing a polyalkylene glycol moiety introduced with a thiol group. This argument is not persuasive since claim 17 is a composition claim and as pointed out above, in Tagawa 221, both protein and polyalkylene glycol were modified with thiol groups and introduced to the liposomes having maleimide groups. Tagawa meets the requirements of instant claim.

The compound is bonded to the surface of liposome and therefore, the reference meets the requirements of claim 18.

The reference uses polyethylene glycol as polyalkylene glycol and therefore, the reference meets the requirements of claim 19.

On col. 4, lines 43-47, Tagawa 221 indicates the use of 2, 4-bis (polyethylene glycol) –6-chloro-s-thiazine (activated PEG II) and therefore, the reference meets the requirements of claim 20.

On col. 4, lines 15-20, Tagawa 221 indicates the degree of polymerization of PEG from 20 to 400 and therefore, the claimed molecular weight of PEG in claims 21 and 22 falls within the range taught by the reference.

On col. 3, lines 52-68 the reference teaches the use of dithiothreitol (sulfur containing compound) to modify the antibody and therefore, the reference meets the requirements of instant claim 23.

Since according to Example 3 in the reference, the drug loaded liposomes are effective in in vivo experiments, the reference meets the requirements of instant claim

32 and since instant claim 33 is a composition claim and not a method claim, the amounts of the drug taught by the reference are deemed to be effective amounts for the treatment of stomach cancer and colon cancer as recited in instant claim 34.

2. Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa cited above.

As pointed out above, Tagawa discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody) and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin (note the abstract, col. 2, line 45 through col. 5, line 27 and examples). Tagawa's does not teach the entire claimed range of the bonded compound and the bonded antibody. However, on col. 4, line 53 et seq., Tagawa teaches the activation of the liposome first, that is introducing excess amount of maleimide groups and then reacting first with the thiol activated antibody and then blocking the remaining maleimide groups on the liposomes with excess amount of thiol modified PEG. Furthermore, in Example 2 on col. 7, Tagawa uses 5 mg of Fb' per hundred mg of lipid and this amount is instantly claimed 5 mg per 100 mg lipid. From these teachings, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the thiol activated antibody, since this amount depends upon the amount of the corresponding receptors on/in the host cell and then block the rest of the maleimide groups on the liposomes with the thiol modified PEG. Instant invention therefore, is deemed to be an obvious extension of prior art's teachings.

Applicant's arguments have been fully considered, but are not found to be persuasive. Appellant's arguments for the 103 rejection appear to be similar to those advanced for 102 rejection and based on the unexpected results obtained. Appellant appears to argue that the amounts of PEG in 221 are different from instant amounts. These arguments are not persuasive. A careful review of instant Fig. 2 which shows the concentration of DXR in plasma plateaus at 15 mole percent and therefore, one would expect the same values for DXR even beyond 30 mole percent, that is at the PEG mole percentages in the prior art. Applicant has not shown any unexpected results. Furthermore, as pointed out above, the examiner once again respectfully directs the board's attention to appellant's previous arguments in page 17 of the response dated 8-8-05, "A review of Fig. 3 in applicant's application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids". This statement clearly indicates that irrespective of whether the antibody amount is outside the claimed range or inside the claimed range the results are significant meaning that even 221 results are unexpected. The rejection therefore, is maintained.

Appellant once again argues separately for each of the claims. Since the arguments are similar to those advanced for each of the claims in the 102 rejection which the examiner has addressed separately, the same rationale is deemed applicable even in this rejection.

3. Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin et al (Biochemistry, 1997) of record in combination with Tagawa cited above.

Kirpotin et al disclose sterically stabilized liposome compositions wherein the antibody is conjugated to maleimide terminated membrane anchor lipid. The polymer used is PEG. Kirpotin however, does not indicate the amounts of the antibody conjugated to the lipid in terms of mg per 100 mg lipid, but instead in mg/ml antibody to 7-10 mM liposomes (note the abstract and Material and methods and Discussion sections). Assuming that the amounts are different, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of targeting antibody to obtain the best possible results that is, reaching the target cancer cells expressing the corresponding antigen on the cell surface. One of ordinary skill in the art would be motivated further to vary the amounts since the reference of Tagawa as discussed above, shows that one can bind various amounts of antibody to the bilayer forming lipid. Kirpotin does not teach antibodies other than anti-HER2; however, it is deemed obvious to one of ordinary skill in the art to use any antibody including claimed GAH antibody, which Tagawa (221) uses, since the principle of targeting to the cancer cells is the same. Kirpotin does not teach the treatment of stomach or colon cancer. However, since the liposomes are only delivery devices, it is deemed obvious to one of ordinary skill in the art to choose a specific cancer drug, which is effective against a selected cancer using the liposomes taught by Kirpotin.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed the arguments regarding Tagawa. Applicant's only argument regarding Kirpotin is that it does not overcome the deficiencies of Tagawa. This argument is not found to be persuasive since Kirpotin essentially teaches antibody and PEG bound liposomes and the treatment of cancer just as in instant invention. As pointed out above, applicant has not shown any unexpected results by varying the amounts of the antibody and PEG in prior art's teachings. The unexpected nature of the results obtained using small amounts of the antibody as opposed to those used in Tagawa 221 which appellant argues once again have been addressed above by the examiner.

Appellant once again argues separately for each of the claims in this rejection.

Appellant argues that claim 17 is dependent from claim 16 and the combination of Kirpotin and Tagawa does not teach the combination of the features recited in claim 17. This argument is not persuasive since claim 17 is a composition claim and as pointed out above, in Tagawa 221, both protein and polyalkylene glycol were modified with thiol groups and introduced to the liposomes having maleimide groups. The combination therefore, meets the requirements of instant claim.

The compound is bonded to the surface of liposome in both Kirpotin and Tagawa 221 and therefore, the reference meets the requirements of claim 18.

Both Kirpotin and Tagawa 221 use polyethylene glycol as polyalkylene glycol and therefore, the reference meets the requirements of claim 19.

On col. 4, lines 43-47, Tagawa 221 indicates the use of 2, 4-bis (polyethylene glycol) –6-chloro-s-thiazine (activated PEG II) and therefore, the use of this compound in Kirpotin with a reasonable expectation of success would have been obvious to one of ordinary skill in the art and therefore, the combination of references meets the requirements of claim 20.

On col. 4, lines 15-20, Tagawa 221 indicates the degree of polymerization of PEG from 20 to 400 and therefore, the claimed molecular weight of PEG in claims 21 and 22 falls within the range taught by Tagawa and one of ordinary skill in the art would be motivated to modify the mol. Weight of PEG in Kirpotin because of the teachings of Tagawa with a reasonable expectation of success.

On col. 1, of page 68, Kirpotin teaches the use of mercaptoethanol and on col. 3, lines 52-68 Tagawa 221 teaches the use of dithiothreitol (sulfur containing compound) to modify the antibody and therefore, the combination of references meets the requirements of instant claim 23.

Since according to Example 3 in Tagawa 221, the drug loaded liposomes are effective in in vivo experiments, and the reference of Kirpotin is suggestive of in vivo effectiveness of similar liposomes and therefore, the combination of references meets the requirements of instant claim 32 and since instant claim 33 is a composition claim and not a method claim, the amounts of the drug taught by the references are deemed to be effective amounts for the treatment of stomach cancer and colon cancer as recited in instant claim 34.

4. Claims 16-23, 32-34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hosokawa (6,787,153) or Hosokawa (6,139,869).

Hosokawa in 153 and 869 discloses liposomal compositions wherein the liposomes have maleimide residues on the surface. A protein (monoclonal antibody, GAH and residues of a compound having polyalkylene glycol moiety are bonded via respective groups to the maleimide residues. The liposomes encapsulate the anti-cancer drug, Adriamycin and or other drugs (note the abstract, col. 4, line 47, col. 5, line 39, Examples, examples 7 and 8 specifically and claims in both patents). Since the examples indicate the amounts of the components in terms of mg, it is unclear whether they correspond to the claimed molar amounts. Assuming that they are different, it is deemed obvious to one of ordinary skill in the art to vary the amounts to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Appellant agrees that the HosoKawa 153 and 869 disclose the same amount of antibody and the same amount of PEG as Tagawa 221 and therefore, the issue here is based on the unexpected results. Appellant once again argues that the presently claimed liposomes have unexpectedly have high suppressive effect against tumor proliferation and superior retention in blood as compared with the liposome with the liposome with 5 mg antibody per 100 mg lipids. The examiner in discussing Tagawa 221 reference has addressed these arguments. Since the compositions of Hosokawa 153 and 869 are same as Tagawa, the same response as above is applicable.

Appellant once again argues separately for each of the claims. Since the arguments are similar to those advanced for each of the claims for the rejection of claims over Tagawa 221 reference, which the examiner has addressed separately; the same rationale is deemed applicable even in this rejection.

***Double Patenting***

5. Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,787,153. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in both patented case and instant application are drawn to liposome compositions wherein both an antibody and PEG are attached to the liposome surface through maleimidated terminals of the lipid moiety. Instant claims are generic with respect to the antibody GAH whereas the patented claims are drawn to the antibody fragment of GAH. It would have been obvious to one of ordinary skill in the art that the GAH antibody would behave the same way as the GAH antibody fraction since it contains said antibody fraction. The patented claims are generic with respect to the amounts of the antibody per 100 mg of lipid claimed in instant claims. Amounts are deemed to be obvious manipulatable parameters practiced by an artisan.

Appellant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the examiner must show how the claimed subject matter, not the disclosed subject matter of HosoKawa is being modified to arrive at

appellant's claimed invention. The examiner points out that the double patenting rejection is made on the patented claims and not patent's disclosure. The patented claims are drawn to the same composition, but including active fraction of the monoclonal body of GAH. GAH antibody includes that claimed fraction. Furthermore, the patented claims do not recite any specific amounts with respect to the antibody or PEG and therefore, encompass instant amounts. Appellant's arguments that the rejection merely contends that amounts are deemed obvious manipulatable parameters practiced by an artisan and does not address any of appellant's arguments relating to lack of obviousness with respect to appellant's recited amounts and the unexpected results are not persuasive since as pointed out above, the examiner does not see any unexpected results.

6. Claims 16-23, 32-34 and 37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,139,869. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in both patented case and instant application are drawn to liposome compositions wherein both an antibody and PEG are attached to the liposome surface through maleimidated terminals of the lipid moiety. . Instant claims are generic with respect to the antibody GAH whereas the patented claims are drawn to the antibody fragment of GAH. It would have been obvious to one of ordinary skill in the art that the GAH antibody would behave the same way as the GAH antibody fraction since it contains said antibody fraction. The patented claims are generic with respect to the amounts of the antibody per 100 mg of lipid

claimed in instant claims. Amounts are deemed to be obvious manipulatable parameters practiced by an artisan.

Appellant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the examiner must show how the claimed subject matter, not the disclosed subject matter of HosoKawa is being modified to arrive at appellant's claimed invention. The examiner points out that the double patenting rejection is made on the patented claims and not patent's disclosure. The patented claims are drawn to the same composition, but including active fraction of the monoclonal body of GAH. GAH antibody includes that claimed fraction. Furthermore, the patented claims do not recite any specific amounts with respect to the antibody or PEG and therefore, encompass instant amounts. Appellant's arguments that the rejection merely contends that amounts are deemed obvious manipulatable parameters practiced by an artisan and does not address any of appellant's arguments relating to lack of obviousness with respect to appellant's recited amounts and the unexpected results are not persuasive since as pointed out above, the examiner does not see any unexpected results.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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